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Title

Puberty and asthma in a cohort of Swedish children

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The shift in asthma prevalence from male to female predominance during the pubertal years is believed to result from an increased incidence amongst girls, rather than remission amongst boys [1,2]. Moreover, from the pubertal years onward, airway hyperresponsiveness, a classic feature of asthma, also worsens amongst girls but improves in boys [3]. Asthma medication use, a proxy for asthma severity, follows a similar pattern, with females requiring greater medication from puberty onward [2,4].

These observations support the potential involvement of sex-specific factors with asthma during this period. But, all physical changes of pubertal development cannot be considered equally in relation to asthma, particularly amongst girls. Menarche appears to play a substantial role in asthma presence and timing of onset. Early menarche predicts poorer lung function [5] and higher post-menarchal asthma incidence [6] compared to average/late menarchal age.

To better understand the associations between puberty and asthma, we aimed to assess associations between pubertal staging and asthma symptoms and treatment in a longitudinal, population-based cohort of Swedish children ('BAMSE') born in 1994-96 [7]. The original cohort of 4089 infants was representative of the study catchment area, except higher rates of parental smoking amongst non-responders [7]. Participant characteristics did not differ between those followed through Year 12 and those lost to attrition [8]. At Years 8 and 12, parents completed questionnaires on wheeze frequency in the previous 12 months and asthma medication. Subjects were deemed to have asthma based on parental reports of ≥ 4 episodes of wheeze or ≥ 1 episode of wheeze in combination with inhaled corticosteroid use in the past 12 months. Pubertal incidence of asthma was defined as no asthma at Year 8, but asthma at Year 12. At Year 12, children completed pubertal development questions, based on the composite pubertal scoring system the Peterson index [9, unpublished information from AC Peterson]. Data were collected on 3 measures for both boys and girls (skin changes, linear

growth spurt, pubic hair growth), 2 measures for boys (voice change, beard growth) and 2 measures for girls (breast development, menarche). This scoring system permits for the inclusion of the multiple characteristics of pubertal development along a continuum. For boys, all characteristics contributed equally. Girls reporting menarche by Year 12 were considered to be in late- or post puberty, regardless of other characteristics. Participants were then categorized into one of five mutually exclusive categories: pre-, early-, mid-, late- or post puberty. We further considered menarche independent of pubertal staging.

We used binomial logistic regression to analyse these data and report odds ratios (OR) and corresponding 95% confidence intervals (CI) for unadjusted analyses and models adjusted for confounding by age at Year 12. Analyses were performed with STATA 11.0 (StatCorp LP, College Station, TX, USA). Permission for this study was obtained from the Regional Ethical Review Board of the Karolinska Institutet, Stockholm, Sweden.

At Year 12, the response rate was 82% (3366/4089), with asthma status available for 99% (3339/3366). We excluded those for whom pubertal data were unavailable. This yielded a sample of 2721 (67% of the original cohort), of whom 50.2% were boys.. Nearly all boys (1347/1378; 97.8%) were in pre-, early- or mid-puberty. Nearly half of girls (651/1368; 47.6%) were in late- or post-puberty. Thus, we created sex-specific pubertal staging categories. Boys were trichotomized into pre-, early- or mid/late puberty (none reported post puberty). Girls were trichotomized as pre/early-, mid- or late/post puberty. Approximately half (47.6%) of girls reported menarche by Year 12. Compared to boys, girls had a lower odds of asthma at each assessment (e.g. Year 8: OR 0.66; 95%CI 0.47-0.92; Year 12: OR 0.57; 95% CI 0.42-0.78).

Pubertal staging was not found to be associated with asthma presence vs. absence in boys (Table). In contrast, girls being late/post puberty was inversely associated with asthma at Year 12 (OR 0.35; 95% CI 0.16-0.78). Amongst girls only, the odds of pubertal incidence

of asthma vs. asthma at neither Year 8 nor Year 12 decreased with more advanced pubertal staging (mid-puberty: OR 0.36; 95% CI 0.15-0.88; late/post puberty: OR 0.25; 95% CI 0.09-0.68). Menarche and asthma presence at Year 12 (OR 0.58; 95%CI 0.33-1.02), and menarche and pubertal incidence of asthma (OR 0.56; 95% CI 0.26-1.19) followed a similar trend, although these results did not reach statistical significance. In neither sex was pubertal staging associated with asthma medication use at Yr12.

The widely accepted sex shift in asthma prevalence during adolescence [1,2] was not noted in BAMSE through Year 12. Rather, pubertal incidence of asthma was lower amongst girls than boys (3.0% vs. 5.2%, $p<0.01$), and indeed lower in girls in late/post puberty vs. early puberty. Our results are contrary to others' findings, including a report of a null association between pubertal staging and asthma remission or incidence amongst similar-aged youth [10]. However, their null findings may be partly explained by the low number of participants in late puberty at baseline [10].

We are the first to report on the association between pubertal staging and asthma using a composite and validated measure of puberty classified into one of three mutually exclusive categories. Others have reported on puberty [1]] and timing of menarche [5,6] and asthma. One other group has considered multiple pubertal characteristics in their classification of pubertal staging [10]. However, they considered puberty as a binary outcome: early vs. late puberty [10]. Inclusion of a third category in our establishment of pubertal staging gleans further insight into the understanding of the progression through puberty on asthma presence and incidence during the pubertal years. This provided the opportunity to better elucidate the associations between asthma and puberty than earlier studies.

112 In conclusion, we found an inverse association between puberty and asthma
113 prevalence and incidence for girls only. . Follow-up at Year 16 will glean further insight
114 into these associations as more children reach late- and post-puberty.

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157 **Table. Logistic Regression of Cross-Sectional Associations between Pubertal Staging and Asthma Presence and Pubertal Incidence at**
 158 **Year 12**

| Pubertal Stage | Asthma Presence vs. Absence at Yr12 | | | | | | Pubertal Incidence of Asthma* | | | | | |
|-------------------|-------------------------------------|---------|-------------|-------------------|-------------|-------------------|-------------------------------|-----------|-------------|-------------------|-------------|-------------------|
| | Presence | Absence | Unadjusted | | Adjusted† | | Incidence | No Asthma | Unadjusted | | Adjusted† | |
| Boys | n | n | OR | 95% CI | OR | 95% CI | n | n | OR | 95% CI | OR | 95% CI |
| Pre-puberty | 28 | 321 | | 1.00 | | 1.00 | 16 | 303 | | 1.00 | | 1.00 |
| Early puberty | 59 | 535 | 1.26 | 0.79-2.02 | 1.16 | 0.71-1.90 | 36 | 496 | 1.37 | 0.75-2.52 | 1.37 | 0.73-2.57 |
| Mid/late puberty | 28 | 395 | 0.81 | 0.47-1.40 | 0.67 | 0.36-1.25 | 12 | 368 | 0.62 | 0.29-1.33 | 0.61 | 0.26-1.46 |
| Girls | | | | | | | | | | | | |
| Pre/early puberty | 13 | 148 | | 1.00 | | 1.00 | 9 | 136 | | 1.00 | | 1.00 |
| Mid-puberty | 28 | 523 | 0.61 | 0.31-1.21 | 0.54 | 0.27-1.09 | 14 | 502 | 0.42 | 0.18-1.00 | 0.36 | 0.15-0.88‡ |
| Late/post puberty | 26 | 617 | 0.48 | 0.24-0.96‡ | 0.35 | 0.16-0.78§ | 14 | 576 | 0.37 | 0.16-0.87‡ | 0.25 | 0.09-0.68‡ |
| Menarche | | | | | | | | | | | | |
| No | 41 | 671 | | 1.00 | | 1.00 | 23 | 644 | | 1.00 | | 1.00 |
| Yes | 26 | 617 | 0.69 | 0.42-1.14 | 0.58 | 0.33-1.02 | 15 | 579 | 0.67 | 0.34-1.32 | 0.56 | 0.26-1.19 |

*Asthma incidence from Yr8 to Yr12 vs. no asthma at either Yr8 or Yr12

†Adjusted for age at Yr12

‡p<0.05

§p<0.01